In the German Mesothelioma Registry,[214] the mean age at the time of diagnosis of peritoneal MM was about 59 years for men, whereas women were on average 4 years younger. The mean survival time was about 1 year, but in six of 38 patients longer survival times of up to 7 years were recorded. The epithelial MMs predominated, but no effect on survival time was noticed. The average latency interval was 36 years.

Latency Intervals Between the Commencement of Asbestos Exposure and the Subsequent Diagnosis of Mesothelioma

In the Australian Mesothelioma Surveillance Program, the mean latency interval was 37 years and ranged up to 75 years,[218] and the corresponding latency interval for cases of mesothelioma certified by the Dust Disease Board (DDB) in New South Wales in 2001/2002 was approximately 42 years. In a study of 557 mesothelioma cases reported in 2001 by Bianchi et al.,[219] the latency intervals ranged from 14 to 75 years, with a mean of ~49 years and a median of 51 years. Some authorities and The Helsinki Criteria[220] specify a minimum latency interval of 10 years, whereas others require a minimum interval of 15 years.

Mineral Fibers and Mesothelioma

This section focuses on the relationship between exposures to mineral fibers and the resultant observations of the development of mesothelioma.[1,2] Pleural MMs are most common,[2] although a study of lung cancer and mesothelioma in the pleura and peritoneum among Swedish insulation workers[210] found that "mesothelioma in insulation workers seems to be situated in the peritoneum more often than in the pleura."

Mesothelioma is widely considered an asbestos "marker disease." The report of the Pneumoconiosis Committee of the College of American Pathologists and the National Institute for Occupational Safety and Health (NIOSH)[221] concluded, "malignant mesothelioma of the pleura and peritoneum either are exceptionally rare or never occur in persons not exposed to asbestos."

In fact, Henderson et al.[222] concluded in an overview of attribution of asbestos-related cohorts in Australia that "no threshold of exposure (in other words a level below which there is no effect) has been delineated for asbestos-related malignancies (mesothelioma and lung cancer), but there is some evidence for a threshold for asbestosis and perhaps diffuse pleural fibrosis."

Fiber Length and Mesothelioma

Mineral fibers other than asbestos have been of concern with regard to possible induction of MM in humans.[223] An appreciable concern for exposure to nonasbestos fibers and the risk of producing disease has been based on exposures using animal models where the exposure to the dust was via intraperitoneal route[224–227] or intrapleural implants.[228,229] The common conclusion in these models is that a comparison of risk for the induction of mesothelioma indicates that on a one-to-one basis, a short fiber is less carcinogenically active than a longer, thinner fiber of the same type. Stanton et al.[228,229] acknowledged that some tested fibers that were shorter or thicker also induced mesothelioma. Pott et al.[224–227] concluded the dimensions of fibers are only one factor that enables a fiber to have the ability of inducing mesothelioma.

The Stanton hypothesis[229,230] argues that carcinogenicity is expressed mainly by long thin asbestos fibers, with lengths >5 μm and especially >8 μm, and in the range of 10 to 20 μm, and diameters <0.25 μm. Shorter fibers appear to be less carcinogenic, although it is doubtful that carcinogenicity is restricted to a critical and precise fiber length or diameter.[38] The Stanton model is supported by evidence derived from animal experiments,[231–234] but it seems likely that biopersistence of amphibole fibers may be more important for MM induction than precise fiber dimensions, and data in humans concerning fiber length and mesotheliomagenicity are equivocal.[230,235] Even so, very short-length fibers (<1 μm) appear to have comparatively little carcinogenic activity.

The majority of the existing data from human studies indicates the fibers that are likely to be relocated from the lungs to extrapulmonary sites where mesothelioma develops are short or thin fibers.[236] In studies by Dodson et al.,[236] some longer fibers (>5 μm) were shown to reach the lymph nodes and pleural areas, but the shorter fibers of chrysotile were the predominant fiber type in pleural plaques. This same observation has been made by Sebastien et al.,[237] and by Suzuki and Yuen.[235,238] Suzuki and Yuen also reported short chrysotile fibers in mesothelial tissue. Dodson et al.[239] reviewed the content of omentum and mesentery tissue from occupationally exposed individuals. While there were some longer fibers in these sites where peritoneal mesothelioma develops, the majority of asbestos burden was found to be in the form of short fibers. Boutin et al.[240] did a comparative study of asbestos burden in lung tissue and "black spots" in the parietal pleura. Their finding in the study group was that there was a prevalence of amphiboles in all sites with 22.5% of the fibers ≥5 μm in the "black spots" of pleural tissue. The authors questioned whether this accumulation of fibers indicated a preferred site for mesothelioma and pleural plaques. In a companion paper, Mitchev et al.[241] evaluated the parietal pleura of 150 consecutive necropsies of urban dwellers. The size and intensity of spots were scored and recorded, as were pleural plaques. The report stated that 92.7% of cases had detectable black spots. The study concluded that "there was no relationship between the predominant locations of black spots and hyaline pleural plaques" or the development of mesothelioma.

Nonasbestos and Nonoccupational Mineral Fibers and Mesothelioma

The risk of mesothelioma is not exclusively associated with occupational exposure to asbestos since there are reports of occurrence of mesothelioma in settings where there is no relationship to commercial asbestos exposure. These include reports from Southern Anatolia (Turkey) where causal exposures were suggested as being from environmental "asbestos most consistent with tremolite and actinolite."[242] One other famous internationally recognized area where there are appreciable environmentally induced MMs is in the Cappadocian region of Turkey.[243,244] The explanation for the causal agent in this region is environmental dust deposits of fibrous zeolite-erionite. Rohl et al.[112] found that environmental samples from the villages of Karain, Tuzkoy, and Sarihidir where mesotheliomas had been reported contained not only fibrous zeolite (erionite), but also trace (<3% by weight) to major (≥3% or more by weight) component of asbestos (chrysotile/tremolite). Fibrous outcrops of zeolite are also situated in the Western U.S. Johnson et al.[245] reported in a rat inhalation model that erionite (fibrous zeolite from the Rome, Oregon, area) could induce mesothelioma more rapidly and more frequently than asbestos.

Another example of exposure to a mineral that contains a component now recognized as a causal agent for MM is vermiculite that was mined in Libby, Montana.[246] This material was widely distributed across the U.S. to sites where it was processed into commercial products. This site and the surrounding areas are of concern, as is the "exposure pathway" from mined minerals, shipped minerals, processed minerals, and consumer exposures to asbestos- contaminated vermiculite.[247] Fibrous amphiboles, including tremolite asbestos, which contaminate vermiculite, have resulted in an appreciable loss of life due to asbestos-related diseases in Libby, not only among the miners and others working with processing and delivery of the mineral, but also within the town populace whose only contact was environmental. The previously described exposures reflect only a selected series of exposure to fibrous materials that may stimulate the development of mesothelioma once inhaled.

Identification of Tissue Markers of Past Exposure (Ferruginous Bodies and Uncoated Fibers)

Fibrous minerals in environmental or tissue samples can be assessed and quantitated by light or electron microscopy. To best interpret tissue burden of fibrous dust in individuals diagnosed with mesothelioma, it is imperative that one understands the limitations of detection with various instruments, magnifications, and preparative techniques used in such evaluation. The largest structures seen in tissue that reflect past exposure to fibrous dust (the causal agent for mesothelioma) are ferruginous bodies. These structures are representative of inhaled fibers (>10 μm) that accumulate surface deposits (to varying degrees) of iron coating along the fibrous core. A ferruginous body having a beaded structure with a clear, elongated, transparent, usually straight core is with a high degree of certainty an asbestos body (see Chapter 27).[248] Tissue sections are very insensitive indicators for determining asbestos content since random sampling and random orientation of ferruginous bodies in the plane of the sections require that many sections be reviewed before their presence can be detected, even when the tissue burden is at occupational levels.[249] Roggli and Pratt[249] stated that the sensitivity for quantitating ferruginous bodies increases greatly when the equivalent of many tissue blocks are digested. Several laboratories have defined a burden of asbestos bodies in tissue from the general population that falls in the range of 0 to 20 ferruginous bodies per gram of wet tissue.[250–253]

The use of light microscopy for the detection of uncoated asbestos fibers in tissue is of essentially no value since they are invisible with rare exception. Even when asbestos fibers are numerous only the larger fibers are seen. Langer et al.[254] stated, "The optical microscope delivers a select, biased population" (i.e., larger fibers thicker than 0.5 μm in diameter). The detection and identification of asbestos fibers isolated from tissue can be more readily done with the scanning electron microscope, but with inherent limitations when compared to the capability of the analytical transmission electron microscope (ATEM) as a counting tool,[255] which enables viewing the thinnest/shortest fiber and can confirm a fiber as asbestos based on morphology, elemental composition (chemistry), and crystalline structure (selected area diffraction). The following concepts may be helpful in interpreting data on tissue fiber content in individuals with mesothelioma:

1. The dust burden within a tissue sample represents that portion of the dust that has not been cleared by the time of evaluation. This skews the analysis toward larger inhaled structures, since the smaller ones are more easily cleared over time. This concept is highly relevant for chrysotile, since chrysotile is predominantly inhaled as a short fiber due to its innate physical curvature (Fig. 43.2).
2. The number of isolated ferruginous bodies (morphologically compatible with asbestos bodies) per gram of tissue, determined by tissue digestion, can be reasonably compared between different studies.

3. Low magnification counts of fibers by scanning electron microscopy (SEM) or transmission electron microscopy (TEM) potentially excludes long/thin asbestos fibers, particularly those of chrysotile.[255]

4. An exclusion of fibers <5 μm in a counting strategy, even when the resolution capability of the ATEM is used can result in exclusion of the vast majority of asbestos within tissue samples from lung and, even more dramatically, from extrapulmonary sites.

Much of the chrysotile burden in tissue can be missed due to items 3 and 4.

Studies Defining Mineral Fiber Content in Mesothelioma Patients

In a series of studies using tissue digestion, Roggli et al.[83] quantified ferruginous bodies using light microscopy and detected fibers (>5 μm in length) with SEM. In 25 cases of mesothelioma, Roggli et al. analyzed core material of ferruginous bodies and quantified their numbers per gram of tissue. They found the number of ferruginous bodies fell between the number in tissue from patients with asbestosis and controls. Those cases where ferruginous body counts overlapped with counts found in tissue from the general population often lacked an identifiable occupational exposure to asbestos. The cores of 88 of the 90 ferruginous bodies were found to be amphibole asbestos, with only two asbestos bodies having chrysotile cores.[256] A review of fiber exposures and disease by Roggli[257] concluded, "Mesothelioma may occur with fiber burdens considerably less than those necessary to produce asbestosis." Srebro and Roggli[258] reviewed the tissue burden of five cases with pleural mesothelioma and two with asbestosis. The study found that tremolite asbestos, although not commercially of interest, is a component of some commercially exploited chrysotile veins and vermiculite and talc veins. Their conclusion from the tissue evaluation was that "modest elevations of tremolite content in some of their mesothelioma cases suggest that at least for some susceptible individuals, moderate exposures to tremolite-contaminated dust can produce malignant pleural mesothelioma."

Srebro et al.[259] quantified ferruginous bodies and uncoated fibers in 18 mesothelioma cases in which the tissue burden of ferruginous bodies fell within a "control" population (0–20 asbestos bodies (AB)/g wet tissue). The findings indicated that "electron microscopic analysis of pulmonary mineral fibers may be required to differentiate asbestos-related mesotheliomas from non-asbestos-related cases when AB counts are within the range of background values."

In a synopsis of observations regarding tissue burden from 396 cases of MM, 28 of which were peritoneal, Roggli[260] concluded that the highest levels of fiber burden "occurred in patients who also had asbestosis, which was found in 12% of pleural and 43% of peritoneal cases." He concluded that the average lung fiber burden was higher in peritoneal cases than in pleural cases, a point that is not in agreement with data from our laboratories.[23,261] The observation was also made that approximately 70% of female mesothelioma cases had elevated fiber burden and many had exposure via household contact to an individual with occupational exposure to asbestos. The analysis strategy incorporating SEM included fibers that were detected and were >5 μm in length.

Paoletti et al.[262] reported a high number of pleural mesotheliomas in eastern Sicily. The study included residents who purportedly "never had any relevant exposure to asbestos during their professional lives." However, samples from quarries and building materials commonly used in the area yielded amphibole fibers, as well as the same type of tremolite-actinolite fibers as in lung tissue of a mesothelioma patient. In a similar environmental exposure, Langer et al.[263] reported that four small villages in northwestern Greece had levels of malignant pleural mesothelioma which accounted for "1% of the total mortality from 1981–1985." They reported fibers found in the lungs in individuals with so-called "Metsovo (Greece) lung" consisted of asbestiform tremolite that was identical to the fibers found in the whitewash once used in the area.

Howel et al.[264] reviewed the mineral fiber content and routes of exposure to asbestos associated with mesothelioma in a region of England. They concluded, "The study has confirmed previous results of higher concentrations of asbestos fibers in cases than controls, and has shown that this is still found in subjects with little evidence of occupational and para-occupational exposure. The overlap in concentrations of retained asbestos for different groups of subjects did not suggest a clear cut-off value."

One of the few places where anthophyllite has been mined for commercial utilization is in Finland. Karjalainen et al.[265] reviewed the clinical status of 999 Finnish anthophyllite miners. Three of the individuals died from pleural MM and one from peritoneal mesothelioma. The latency period from onset of employment until diagnosis was from 39 to 58 years. Such a long latency period is not unusual in asbestos-exposed individuals.[23,261] Tissue analysis was conducted on tissue from three individuals with the findings by ATEM being from 270 to 1100 million fibers per gram of dry tissue. This information is important in light of the discussions regarding the carcinogenicity of fibers based on a concept of long/thin fibers being the most dangerous, since individual anthophyllite fibers are among the thickest in diameter of all the amphiboles. Tuomi et al.[266] reported on tissue burden in 19 mesothelioma cases and 15 randomly selected autopsy cases from Finland. The technique used SEM analysis of lung tissue. The "fiber concentration ranged from 0.5 to 370 million fibers per gram of dry tissue in the mesothelioma group and from <0.1 to 3.2 million fibers per gram of dry tissue in the autopsy group. . . . In the lungs of the six mesothelioma patients, anthophyllite was the main fiber type."

While most reports of individuals with MM involve a long period from first exposure, there are reports of mesothelioma developing in young people. Andrion et al.[267] reported a case of peritoneal mesothelioma in a 17-year-old boy. They analyzed lung tissue and found 510,000 asbestos fiber per gram of dry lung tissue, of which 62% were chrysotile and 38% were tremolite. It was suggested that "the tremolite fibres were probably due to environmental exposure to contaminated cosmetic talc."

Glickman et al.[268] reported a study of 18 histologically confirmed cases of canine mesothelioma. The "lung tissue from three dogs with mesothelioma and one dog with squamous cell carcinoma of the lung had higher levels of chrysotile asbestos fibers than lung tissue from control dogs." Such findings raise the question as to whether environmental/secondary exposures to mineral fibers in family members were similar to that of their pets.

It is appropriate to focus on publications that have reviewed mineral fiber content in mesothelioma cases from Canada since 90+% of asbestos used in commercial products in the U.S. came from mines in Canada. Canadian chrysotile has been reported to have a small component of fibrous tremolite asbestos. An evaluation for tremolite was conducted on a *Union Internationale Contre le Cancer* (UICC-B) sample of chrysotile. This sample was composed of chrysotile obtained from several mines in Canada with the percentage based on percent of total mined commercial product. Over 20,000 fibers were analyzed by ATEM and all asbestos fibers observed were chrysotile.[269] This finding is of considerable importance since chrysotile has been shown to induce mesotheliomas in animal models.[227,270] There is confusion as to the ore of which mines contain tremolite and what percent is tremolite.[271] Adding to the confusion is the doctoral dissertation by De[272] stating that crocidolite existed in the adjacent mineral formations to the mined veins of chrysotile.

There are several publications with the same theme regarding chrysotile and risk of MM. Churg[273] evaluated what he considered to be 53 "acceptable" cases of chrysotile-induced mesothelioma, 41 of which were in individuals exposed to chrysotile mine dust that was considered by Churg to be naturally contaminated with tremolite. Ten cases were in individuals who worked in industries where "suspicion of amosite or crocidolite contamination [was] high." His conclusion at that time was that "although chrysotile asbestos can produce mesothelioma in man, the total number of such cases is small and the required doses extremely large." He further concluded,

> The data [were] consistent with the idea that mesotheliomas seen in chrysotile miners and some secondary industry workers [was] produced by the tremolite contained in the chrysotile ore, but that the short length and low aspect ratio of the tremolite [made] its carcinogenicity quite low. However, these data are very indirect, and a role for the chrysotile fiber itself is still possible.

In another study from Churg et al.'s[274] laboratory, an evaluation of lung tissue from 94 long-term chrysotile miners and millers from the region of Thetford Mines, Quebec, was conducted. The conclusion was that "mesothelioma, airway fibrosis, and asbestosis were strongly associated with a high tremolite fiber concentration, whereas pleural plaques and carcinoma of the lung showed no relationship to tremolite burden." They stated,

> Total fiber size measures (total fiber length/g and others) showed differences similar to fiber concentration for mesothelioma, airways fibrosis, and asbestosis, but no one measure was clearly better than another or better than fiber concentration. We conclude that, in this population of heavily exposed chrysotile miners and millers, the presence of airways fibrosis and asbestosis and, probably, mesothelioma reflects high tremolite burden. Whether chrysotile fibers themselves play a role in disease induction remains uncertain.

Another report from Canada evaluated the fiber content in 50 workers seeking compensation from the Workers' Compensation Board of Quebec for pleural or peritoneal mesothelioma.[275] Twelve in the study group were from Asbestos Township (chrysotile mining region) and 11 were from the chrysotile mining region of Thetford Mines. The remaining 27 worked in various nonmining industries. The fiber types found in the three groups were different: "The lungs of workers from Thetford Mines [contained] only chrysotile and tremolite; those from Asbestos Township [contained] chrysotile, tremolite, amosite, and crocidolite; and those in other industries [contained] largely amosite and crocidolite."

Begin et al.[276] reviewed 120 cases referred to the Quebec Workman's Commission Board for work-related compensation of industrial disease. The individuals were divided into three groups. The first consisted of 50 cases from the manufacturing and industrial application sector (primary industry, group 1); 50 cases from the manufacturing industrial application sector (secondary industry, group 2); and 21 from industries where asbestos was not a major work material, often an "incidental" material (tertiary industry, group 3). They reported

> [the] incidence of new cases in each group documenting the general incremental trend in all groups, with the sharpest rises in group 3. In the mining towns of Thetford and Asbestos, the incidence of mesothelioma was proportional to the workforce, thus suggesting that the tremolite air contamination, which [was] 7× higher in Thetford, may not be a significant determinant of the disease in these workers. The incidence of the disease in these chrysotile miners and millers was 62.5 cases per million

per year for the 1980–1990 period in Quebec. The incidence of pleural mesothelioma in chrysotile miners and millers, although not as high as in crocidolite workers, [was] well above the North American male rate. Comparative analyses of incidence of the disease in the two mining towns suggest that tremolite contamination may not be a determining factor in these chrysotile workers.

Langer and McCaughey[277] analyzed lung tissue from an individual whose "sole exposure to asbestos was to chrysotile form during brake maintenance and repairs." Contrary to the concept that chrysotile clears from the lung, these investigators found unaltered chrysotile in the analysis in the form of chrysotile fibrils <1 μm and some >5 μm in length. There were no amphiboles found in the tissue; thus the data were consistent with the occupational history of exposure.

Nolan et al.[278] evaluated the fiber burden by ATEM in five lung cancer cases from Quebec, Canada, and one case of an American worker who developed pleural mesothelioma. Interestingly, the predominant fiber type in the tissue from the American worker was chrysotile, and it was present at a "concentration of 300 times that of the average total fiber content of the Canadian case." Furthermore, "the fiber length distribution of the chrysotile recovered from the U.S. mesothelioma case was indistinguishable from that of chrysotile specimens known to produce mesotheliomas in rats. It was also found that the characteristics of the calcium-magnesium-iron silicate fibers present in all six cases were not readily comparable to tremolite asbestos specimens known to induce mesotheliomas in animals." The longest chrysotile fiber found was 33 μm, with 99% of the fibers identified being chrysotile. No commercial amphiboles were found in the analysis and only 1.5% of the 883 fibers sized were reported as being ≥5 μm in length. An important observation was made that when studies report findings based on fibers ≥5 μm in length, a bias toward tremolite may be introduced since the fiber length distributions in this study indicate a difference between chrysotile and the CaMgFe fibers found in the samples. Eleven percent of the latter were ≥5 μm in length, and the mean of the three reference chrysotile specimens was 1.3%.[278]

Churg and Vedal[279] evaluated tissue samples from 144 shipyard workers and insulators in the Pacific Northwest. Amosite (the majority fiber type) was reported to be found in all lungs, while tremolite and chrysotile were found in most lungs. "No relationship was found between the concentration of chrysotile or tremolite and any disease. Analysis of fiber size measures (length, width, aspect ratio, surface, mass) showed that pleural plaques were strongly associated with high aspect ratio amosite fibers and suggested mesotheliomas were associated with low aspect ratio amosite fibers." They concluded that differences in fiber burden and disease exist when comparing mesothelioma in chrysotile miners and millers and shipyard workers, in that mesothelioma appears to occur at much lower amosite burdens than does asbestosis, "in contrast with the situation previously reported for chrysotile-induced mesothelioma."

McDonald et al.[280] reported on the fiber content of lung tissue from individuals with mesothelioma who were 50 years of age or younger at time of diagnosis. There were 69 males and four females. "Incremental risk examined in a linear model was as highly significant for all amphiboles together as individually. Short, medium and long amphibole fibers were all associated with increased risk in relation to length. In this young age group, amosite and crocidolite fibers could account for about 80% of cases of mesothelioma, and tremolite for some 7%." There was some increased risk with chrysotile, but that was determined to fall short of statistical significance.

Leigh and Driscoll[193] reviewed cases of MM in Australia. They reported that Australia had a history of asbestos mining extending over 100 years, and Australia was the world's highest user per capita of asbestos in the 1950s, with the highest reported national rates of mesothelioma in the world. A review of tissue burden in cases of mesothelioma without documented exposure to asbestos found asbestos in 80% of lung fiber burdens as determined by ATEM of >200,000 fibers >2 μm length per gram of dry lung. They noted the high rate of MM in Australia was related to high past use of asbestos, which was reflected in the findings of elevated tissue levels from previously unrecognized exposures.

Workplace exposures to asbestos often involve exposure to several types of asbestos. There are several reported settings where exposures are overwhelmingly limited to one type of asbestos. Such occurred in facilities where manufacturers were creating filters for cigarettes from crocidolite asbestos. In 1987 Talcot et al.[281] reported that mesotheliomas had been observed in three employees in such a facility. In 1989 Talcot et al.[282] reported that 15 of 33 deaths associated within the cohort were from cancer and five were due to MM. Tissue was referred to our laboratory from two individuals who worked in the facility and died from pleural mesotheliomas.[283] The lung tissue from each individual was found to contain large numbers of ferruginous bodies as well as asbestos fibers, the vast majority of which were crocidolite. Nearly all of the ferruginous bodies analyzed also had crocidolite cores. Dodson and Hammar[284] reported a case in which a housewife developed pleural mesothelioma and the only known contact with asbestos was a history of smoking crocidolite-filtered cigarettes. Crocidolite fibers were identified by ATEM in digested samples from this individual's lung and lymph node tissue, in which anthophyllite and tremolite fibers were also found.

Another rather isolated exposure to a type of mineral fiber (amosite asbestos) occurred in an asbestos pipe insulation plant. The uniqueness of the exposure was that no other type of asbestos was ever documented as having been used in this isolated facility. Levin et al.[285] reviewed the status of former workers in the facility and determined that as of 1998, there were four deaths from pleural mesothelioma and two from peritoneal mesothelioma among a cohort of 1130 individuals. An interesting aspect of employment at the facility was that, historically, individuals often worked for only short periods of time before leaving the facility.

We have published findings in over 200 cases of mesothelioma referred to our labs for evaluation. Ferruginous body concentrations and uncoated asbestos fiber burden as defined on a count scheme by ATEM included fibers >0.5 μm in length. Dodson et al.[23] evaluated the asbestos content in 55 mesothelioma cases from the Northwestern U.S. The area has appreciable heritage in shipbuilding and repair, and thus it was not a surprise that the most common finding was amosite fibers in all but two lung samples (96.4%); 18 individuals had over one million amosite fibers per gram of dry tissue, and 46 of the 55 individuals had an average asbestos body burden of over 1000 asbestos bodies per gram of dry tissue. Analysis of the cores of ferruginous bodies indicated that most were formed on amphiboles: 92.9% were found to have amosite cores, 2.9% crocidolite cores, 1% tremolite cores, 0.4% anthophyllite cores, 0.4% actinolite cores, and 0.1% chrysotile cores. The common observation was that the positive lung samples often reflected a mixed asbestos exposure. The other commercial asbestos fibers were crocidolite in 40% of cases and chrysotile in 56.4% of cases. Five cases were diagnosed as having a primary mesothelioma of the peritoneum. Peritoneal mesotheliomas have traditionally been associated with a higher asbestos burden than pleural MMs. However, the five cases in this study did not follow this pattern, showing a range from high fiber burden to very low fiber burden. In another study by Dodson et al.,[261] cases of peritoneal mesothelioma did not follow the general rule of association with the highest fiber burdens.

A possible explanation for the relatively low fiber counts by Dodson et al.[261] may lie in the manner in which the counts were performed. Most asbestos fibers in human lung are less than 5 μm in length and are therefore not reported in many studies that include only the longer or thicker population of fibers in lung tissue. Both studies concluded that most fibers found in the lung tissue would not have been seen if screened by light microscopy or SEM.[23,261] The study from the Northwest cohort also found that 26 of the cases had appreciable ferruginous body and uncoated fiber burdens but did not have pathologically definable asbestosis.[23] All but three cases from the Northwestern cohort had levels of ferruginous bodies higher than that considered in our laboratory as representing general population levels (20 ferruginous bodies per gram of wet tissue). However, in the second study, 13 cases had ferruginous body levels within those considered as reflective of tissue from the general population.[261] This implies the importance of combining the data regarding uncoated fiber burden and ferruginous body burden when attempting to define past exposure and a causal relationship of that exposure to asbestos and mesothelioma.

A similar trend was seen in a study of tissue burden of ferruginous bodies and uncoated asbestos fibers in 15 cases of mesothelioma in women[286]; 13 of 15 samples contained ferruginous bodies and, as with the two previous studies, amosite was the most commonly found form (80% of cases). However, unlike the other studies, the second most commonly found form of asbestos was tremolite (60% of cases). There was a considerable drop in overall tissue burden of uncoated asbestos fibers in the lower half of the study group when compared with the levels found in the lower half of the other two mesothelioma study groups. Seven individuals had bystander exposure from contact with contaminated clothing of a spouse or family member.

The common findings in all three study groups were the presence of mixed types of asbestos. The lung tissue in some cases of mesothelioma in each group had low overall tissue burden of asbestos.

The transport and deposition of asbestos fibers in extrapulmonary sites was evaluated in another study from our laboratory.[239] These individuals resided in the shipyard building/repair areas of the Northwest. Ferruginous bodies were found in 18 lung samples, five mesentery samples, and two omentum samples. The common fiber type in the lung (95% of cases positive), mesentery (65%), and omentum (70%) was amosite. Chrysotile was found in 50% of lung samples. Chrysotile was the second most common form of asbestos found in the extrapulmonary sites; 25% of the mesentery and three omentum samples were positive for chrysotile. Crocidolite was found in 25% of lung samples, 15% of mesentery samples, and 5% of the omentum samples. In the amosite-exposed individuals, the predictors of the likelihood of finding an asbestos fiber in the extrapulmonary sites included the presence and numbers of ferruginous bodies and total asbestos fibers in the lung. The relevance of the findings was couched in the fact that the individual studies had appreciable amphiboles in the lung tissue and the parameters may well change in a heavily exposed chrysotile cohort.

Mesothelioma is a rare tumor that, based on the previous data, clearly is related to the exposure to fibrous minerals, and in most instances, Peto et al.[287] correctly observed, "the great majority of mesotheliomas are caused by asbestos" and a "country's mesothelioma rate is therefore a quantitative indicator of its population's past exposure—mainly occupationally—to asbestos."